REMARKS

The claims have been amended for clarification, in at least partial response to the criticisms of the Office, and to distinguish the disclosure of Nie, *et al.* As agreed at the interview, the limitation that the second signal generating moiety consists of a single fluorophore (rather than a fluorophore plus a quencher) clearly distinguishes the constructs coincidentally disclosed by Nie. The compositions described in the present application have never contained quenchers as part of the second signal generating moiety. No new matter has been added, and entry of the amendment is respectfully requested.

The Rejections Under 35 U.S.C. § 112, paragraph 2

All of the criticisms in the more than two pages of items are directed to the wording of claim 1 except for two specific criticisms of claim 2. Although applicants believe that claim 1 as it previously stood was clear, certain amendments have been made in response and each of the specific criticisms is discussed below.

The asserted lack of clarity of the word "each" in line 2 as referring "an ordinal distinction or a distinction of class type" is not understood by applicants, so applicants are unable to amend the claim in response. "Each" refers to each type of the different types of label in the composition.

The asserted unclarity of "which" in line 2 has been addressed by amendment, by adding "support" after "which."

The objection to "both" in line 2 has been obviated by deleting this term. The criticism of claims 1, lines 2-5, is not understood. Perhaps this is remedied by deleting "both" from line 2.

The referent of "which" in line 3 has been clarified as referring to the "moiety." The meaning of the word "together" in line 4 is obviated by its deletion.

Applicants do not understand the criticism of "characterizing signal" in lines 4 and 9, perhaps the addition of explanation in the second to last paragraph of the amended claim "which characterizing signal characterizes the label" provides sufficient clarity.

It is believed evident that "said label" in line 4 refers to "each different label," that "all of said different labels" does indeed refer to all of them in lines 6-7 and the term "labels" has been replaced by "each label" in line 10.

The use of the term "second" in line 5 is conventional claim language to distinguish from the "first" signal generating moiety characterizing the label in part (a). The referent of "which" in line 6 has been specified.

Applicants are unable to perceive the difficulty with respect to "all said different labels" as set forth in the Office action.

The objected to phrase in lines 6-7 has been deleted, as have the terms "clamped" and "value" in line 7.

The objection to "each" in line 7 is mooted by the deletion of the contained phrase. Antecedent basis has been supplied for "one or more wavelengths." The referent of "which" has been supplied in line 9.

The terms "permit" and "them" have been eliminated from line 11, as have been "to interact" and "desired."

Applicants believe that they have meticulously addressed each of the bases for objection to claim 1.

As to claim 2, the amendment to claim 1 supplies the antecedent basis for "said characterizing signal generating moiety." The referent of "each" in line 2 is clearly "the entities."

In view of the foregoing amendments and discussion, the rejection under 35 U.S.C. § 112, paragraph 2, may be withdrawn.

The Rejection Under 35 U.S.C. § 102

Claims 1-4 and 7 were rejected under 35 U.S.C. § 102(e) as assertedly anticipated by Nie, *et al.* (U.S. Pub. No. 2003/0148544). Applicants appreciate the recognition by the Examiners at the interview that the now added limitation that the second signal generating moiety "consist of" a single fluorophore distinguishes Nie. Nie appears to describe a type of label which may or may not be useful in the method described therein. Nie describes a stem/loop oligonucleotide probe where the ends of the stem become separated when the loop binds to a target nucleotide sequence. The separation of the ends of the stem permits detection of a fluorophore contained on one end of the stem from a quencher on the other end of the stem. The emission of the signal indicates that binding has occurred. According to Nie, attached either to the fluorophore or quencher is a multihued bead.

The system described by Nie clearly is distinguished from the present invention. The present invention excludes the possibility that the second signal generating moiety, which indicates the presence of the target, could include a quencher - an essential element of the Nie system. Further, Nie does not suggest the present invention as it operates on an entirely different principle. The system of Nie depends on the interaction of the stem/loop region of the construct with the target so as to separate a fluorophore from its corresponding quencher. Thus, Nie's system is, in effect, limited to detection of oligonucleotides. The system of the invention, on the other hand, relies on detection of a fluorophore whose emission is constant regardless of whether a target has been contacted. The presence or amount of the signal from this fluorophore simply provides a counter for the number of labels that are present at a given location. It does not rely on a change in the structure of the label for emission of a signal indicating that target is present.

It is assumed that the Nie system could be used in only contexts where a multiplicity of nucleic acid targets are spaced over a volume or area. The emission of a signal from a specific location would indicate that a sequence corresponding to the stem/loop structure is present at that location. In the method of the invention, on the other hand, the characterizing signal already serves this function; the second signal generating moiety serves to count the number of labels associated with the target and to resolve ambiguities that might be created by the method of constructing the characterizing signals, as described in the specification in detail on pages 5-6, bridging paragraph.

Accordingly, Nie neither anticipates nor renders obvious the present invention.

The Rejection Under 35 U.S.C. § 103

Claims 5-6 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Nie in view of Kauvar *et al.* (U.S. Pub. No. 2001/0044116). These claims are patentable for the same reasons set forth above with respect to claims 1-4 and 7. However, applicants believe the Office has not delineated any motivation to combine these documents that satisfies the criteria set fourth in *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998). There is no motivation, and a good deal of difficulty in applying the Nie method to intracellular environments since the Nie method is designed to detect only nucleotide sequence targets. It is only the complexity with which the present invention is capable of dealing that makes intracellular environments of particular interest. And clearly, as to claim 6, neurocircuitry is virtually devoid of any nucleotide sequence targets of interest.

Conclusion

The discussion at the interview was most helpful in clarifying the manner in which the compositions of the present invention could effectively be claimed so as to distinguish them from the coincidental overlap with the Nie publication. The claims have been amended accordingly. Therefore, it is believed that all claims herein, claims 1-7, are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 388512010900.

Dated: January 4, 2006

Respectfully submitted,

By Kate H. Murashige
Kate H. Murashige
Registration No.: 29,959
MORRISON & FOERSTER LLP
12531 High Bluff Drive
Suite 100
San Diego, California 92130-2332
Telephone: (858) 720-5112
Facsimile: (858) 720-5125